REMARKS

Summary of Telephonic Interview

Applicant wishes to thank Examiner Olson for taking the time to discuss this Office Action with the undersigned representative and colleague Sylvia Georges via the telephonic interview which took place on September 15, 2009. The substance of the interview has been included in this response. During the telephonic interview Applicant's undersigned representative proposed claim amendments (outlined below) to overcome the rejections made under 35 U.S.C. § 112. Applicant also discussed the cited references, *i.e.*, Wright *et al.*, Gilbert *et al.*, Naesens *et al.*, and Hostetler, and presented arguments regarding lack of motivation to combine acyclovir, gancyclovir or cidofovir[1] with a thymidine kinase inhibitor and data demonstrating Applicant's findings of unexpected results to overcome the 35 U.S.C. § 103 (a) rejections; these arguments are included in the contents of this response.

Claim Amendments

Applicant has cancelled claims 2-9, 20-31, 33-35, and 47-50, and amended claims 1, 11-13, 32, 37-40, and 43-46, without prejudice.

Specifically, Applicant has removed the term "analog" from claims 1 and 32. Applicant has also removed a reference to solvates from claims 1, 11-13, 32, 37-40, and 43-46.

Claims 1, 32, 43 and 45 as amended herein recite the specific Herpes simplex virus thymidine kinase inhibitor, 2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine ("HBPG"); the specific antiherpes substances, acyclovir monophosphate, ganciclovir monophosphate, cidofovir, and foscarnet.

Claim 39 as amended recites a kit comprising the specific Herpes simplex virus thymidine kinase inhibitor, HBPG, and the specific antiherpes substance, acyclovir.

---

[1] Applicants would like to point out that brivudin is incorrectly mentioned in the Examiner's interview summary and that this specific antiherpes substantces was not one of the antiherpes substances discussed during the interview. The antiherpes substances discussed were acyclovir, ganciclovir, cidofovir, and foscarnet.

Claim 40 as amended recites a combination of the specific Herpes simplex virus thymidine kinase inhibitor, HBPG, and the specific antiherpes substance, acyclovir. Pursuant to a restriction requirement, claims 41 and 42 have been withdrawn. Applicant requests rejoinder thereof upon a finding of allowability of independent claims 1 and 32.

Support for the claim amendments can be found throughout the application as filed, *e.g.* at paragraphs [0009], [0011], and paragraphs [0048] through [0059] of the published application (US 2004/0259832), *inter alia.*

Thus, claims 1, 10-19, 32, 36-40, and 43-46 are now presented for examination. No new matter has been added.

Claim Rejections

Rejection under 35 U.S.C. §112, First Paragraph

Claims 1, 2, 7, 8, 14-19, 32, 34, 39, 40, 50 are rejected, the Office states:

> because the specification, while being enabling for one of a composition comprising 2-phenylamino-6-oxo-9-(4hydroxybutyl)purine with an antiherpes substance such as foscarnet, acyclovir, ganciclovir, does not reasonably provide enablement for the use of a combination of an inhibitor of Herpes simplex virus thymidine kinase with any antiherpes substance comprising one or more of a pre-phosphorylated or phosphonate nucleoside analog, a pyrophosphate analog and a nucleoside analog or esters of said drugs (Office Action, page 9-10).

Applicant respectfully disagrees with the grounds for this rejection; however in order to expedite prosecution, Applicant has amended independent claims 1 and 32 to specifically recite a composition comprising the Herpes simplex virus thymidine kinase inhibitor, 2-phenylamino-6-oxo-9-(4hydroxybutyl)purine (HBPG), and the specific antiherpes substances foscarnet, acyclovir, cidofovir, and ganciclovir. Applicant notes that the Examiner has conceded (above) that the combination of HBPG plus acyclovir and ganciclovir are enabled; a person having ordinary skill in the art would consider a composition comprising HBPG and cidofovir also to be enabled based on the present disclosure at page 14, Table 4 of Example 3, which shows that cidofovir and HBPG work, and the fact that, unlike acyclovir and ganciclovir, cidofovir is a nucleoside analog with a similar mechanism of antiviral action. In view of the foregoing,

Applicant requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, First Paragraph.

Rejection under 35 U.S.C. §112, Second Paragraph

Claims 1-3, 5, 7, 8, 10-19, 32-34, and 36-40 were rejected as allegedly indefinite for reciting the term "analog" in the claims.

Applicant respectfully disagrees with the grounds for this rejection; however, in order to expedite prosecution, Applicant has amended the claims as follows.

First, Applicant has removed the term "analog" from independent claims 1 and 32.

Second, Applicant has amended claim 1 to recite the specific Herpes simplex virus thymidine kinase, 2-phenylamino-9-(4-hydroxybutyl)-6-oxopurine. Applicant has also included the specific pre-phosphorylated and phosphonate nucleoside analogs, acyclovir monophosphate, ganciclovir monophosphate, and cidofovir. In addition, claim 1 recites the specific pyrophosphate analog, foscarnet.

In view of the foregoing, Applicant requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph.

Rejections under 35 U.S.C. §103(a) –Wright et al. in view of Gilbert et al.

Claims 1-3, 7, 8, 10, 14, 16-18, 32-34, 36, 43, 45, and 50 were rejected as being allegedly obvious over Wright *et al.* (U.S. Patent No. 5,646,155) in view of Gilbert *et al.* (Gilbert *et al. Drug Resistance Updates* 5 (2002) 88-114).

In particular, the Office Action states:

> It would have been obvious… to make a composition comprising a combination of an inhibitor of Herpes Simplex virus thymidine kinase and an antiherpes substance… since Wright et al. discloses pharmaceutical compositions comprising a herpes simplex virus thymidine kinase inhibitor and suggests the combination with other direct antiviral drugs.
> One of ordinary skill in the art would have been motivated to make a combination… since Wright suggests combination… one of ordinary skill in the art would have reasonably expected that the combination… would have resulted

in substantially similar or beneficial effects in the treatment of herpes infections (Office Action, page 4).

Applicant respectfully disagrees, for at least the following reasons.

Lack of Motivation to Combine

First, Wright *et al.* discloses HBPG, an inhibitor of Herpes simplex virus thymidine kinase ("HSV-TK"), but does not teach or suggest combining HBPG with any specific inhibitor of viral DNA replication. Wright *et al.* at column 9, lines 59-63 makes only a vague reference to a "combination with other active ingredients, *e.g.*, direct antiviral drugs, growth factors which could facilitate neuronal survival in neurological diseases of peptidase or protease inhibitors."

Gilbert *et al.* discloses the nucleoside analogs acyclovir and ganciclovir; the nucleoside phosphonate analog, cidofovir; and the pyrophosphate analog, foscarnet. There is no mention in Gilbert *et al.* of using a HSV-TK inhibitor such as HBPG. Gilbert *et al.* also describes the mechanism of action for these nucleoside and pyrophosphate analogs. According to Gilbert *et al.* "[a]cyclovir... and ganciclovir are deoxyguanosine analogues that must be phosphorylated to their triphosphate form to exert their antiviral activity. The thymidine kinase of HSV... phosphorylate[s] these compounds to their monophosphate form (Gilbert *et al.*, page 89, left hand column, first full paragraph, emphasis added).

Neither Gilbert *et al.* nor Wright *et al.* suggests or teaches combining one of the above-mentioned nucleoside and pyrophosphate analogs with a HSV-TK inhibitor. Nucleoside analogs that require phosphorylation by thymidine kinase for activation, as do acyclovir and ganciclovir, would not be expected to work in combination with HBPG, which inhibits thymidine kinase phosphorylation. Thus, there would be no reason to combine acyclovir or ganciclovir with an inhibitor of HSV-TK such as HBPG, at least because one of ordinary skill in the art would not expect this combination to work and therefore, would not be motivated to combine these two classes of compounds. In fact, based on this fact, one of skill in the art would consider Gilbert et al. as teaching away from the present invention.

Unexpected Results/Synergism

In addition, Applicant has discovered that, quite surprisingly, combinations of an inhibitor of HSV-TK and the recited antiherpes compounds have unexpected synergistic activity against HSV during *in vivo* studies (see, *e.g.*, paragraphs [0007] and [0043]-[0055] of the present application, published as US 2004/0259832), and the following discussion.

The present application provides clear evidence of unexpected results. For example, at paragraph [0049], the application describes experiments with respect to a combination of HBPG and foscarnet (emphasis added).

> The results of Table 1 establish dose-response relationships for the effect of each compound when administered individually to mice to be used against encephalitis caused by HSV1 and HSV2. **The results of Table 2 illustrate the effect of combining suboptimal doses of HBPG and foscarnet in treatment of HSV2 encephalitis, showing clear synergistic effect of the combinations. For example, the combination of 50 mg/kg of each compound protected 50% of mice from HSV2 encephalitis, whereas simple addition of the compound effects would be expected to protect only 10% of animals. The combination of 100 mg/kg of HBPG and 50 mg/kg of foscarnet protected 80% of mice from HSV2 encephalitis, whereas simple addition of the compound effects would be expected to protect 30% of animals.**

The data described in Example 3 also shows clear evidence of unexpected results for combinations of HBPG and foscarnet, acyclovir, or cidofovir, as follows.

First, the data in Table 2 demonstrate a clear synergism between foscarnet and HBPG rather than an additive effect as is thought by the Examiner. Treatment of HSV2 encephalitis in mice with 100 mg/kg HBPG alone protected only 30% of mice and that 50 mg/kg of foscarnet did not protect any mice (0% survival). In contrast, a combination of 100 mg/kg of HBPG and 50 mg/kg of foscarnet protected 80% of mice from HSV2 encephalitis. This is not simply an additive effect, but rather a synergistic effect resulting in an almost 3 fold increase in survival (30% expected, 80% obtained).

Second, the data in Table 4 demonstrate a clear synergistic effect between cidofovir and HBPG. Treatment of HSV1 and HSV2 encephalitis in mice with 50 mg/kg HBPG only

protected 10% of mice and 2.5 mg/kg of cidofovir protected 30% of mice from HSV1 encephalitis and 40% from HSV2 encephalitis. An additive effect would have only yielded a 40% survival rate for mice infected with HSV1 encephalitis and a 50% survival rate for mice with HSV2 encephalitis. In fact, a combination of 50 mg/kg of HBPG and 2.5 mg/kg of cidofovir protected 90% of mice from HSV1 encephalitis and 100% of HSV2 encephalitis. This is a doubling in survival rates for mice with HSV1 and greater than 2-fold increase in survival for mice infected with HSV2 encephalitis. Thus, this combination therapy is clear proof of synergism.

Third, the data in Table 6 clearly demonstrate that combining HBPG with acyclovir produces a synergistic effect. Treatment of HSV1 encephalitis in mice with 100 mg/kg HBPG only protected 30% of mice and 50 mg/kg of acyclovir only protected 30% of mice infected with HSV1 encephalitis. An additive effect would have only yielded a 60% survival rate. In contrast, a combination of 100 mg/kg of HBPG and 50 mg/kg of acyclovir protected 100% of the mice. Therefore, this is not simply an additive effect, this is clearly a synergistic effect.

These synergistic and unexpected results disclosed in Example 3 are exactly the type of evidence the U.S. Supreme Court has suggested are useful to rebut an obviousness rejection in KSR v. Teleflex, 550 U.S. 398, 127 S. Ct. 1727 (2007). Thus, Applicant respectfully submits that these unpredictable results render the claimed inventions patentable, and respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. §103(a) –Wright et al. in view of Hostetler

Claims 1-3, 5, 7, 8, 11-14, 15-18, 32-34, 37-40, and 43-50 were rejected as being allegedly obvious over Wright *et al.* in view of Hostetler (US 5879700).

Specifically, the Office states:

> One of ordinary skill in the art would have been motivated to make a combination of an inhibitor of herpes simplex thymidine kinase and another antiherpes agent since Wright suggests combination of a oxo-guanine thymine kinase inhibitor with other antiherpes agents, and Hostetler discloses other active agents that can be administered topically (Office Action, page 6-7).

The Office Action alleges that one skilled in the art would have combined an oxo-guanine thymidine kinase inhibitor with other antiherpes agents based on Wright *et al.* in combination with Hostetler. Applicant respectfully disagrees, for at least the following reasons.

Wright *et al.* specifically recites the combination of the 9-substituted-N^2-phenylguanine compounds with "direct antiviral drugs," (Wright *et al.*, column 9, line 61). In contrast, Hostetler teaches topical therapies for HSV infections using acyclovir in combination with interferon or a ribonucleotide reductase inhibitor. According to Hostetler:

> The antiherpes virus activity of ACV (acyclovir) in cells occurs with low toxicity because ACV is selectively phosphorylated by HSV thymidine kinase, but not host cell thymidine kinase. As a consequence, only cells infected with HSV can form ACV monophosphate (ACV-MP). ACV-MP is then anabolically converted by cellular enzymes to ACV triphosphate, the active agent that interferes with viral replication (Hostetler, column 1, lines 26-35).

Thus Hostetler teaches that the low toxicity exhibited by acyclovir is attributed to acyclovir's total dependency on HSV-TK for phosphorylation. Hostetler does not teach or suggest combining acyclovir with an HSV-TK inhibitor – as noted above, if anything, Hostetler teaches away from such a combination. One skilled in the art would not have combined Hostetler with Wright *et al.* at least because one of ordinary skill in the art would not expect the combination of acyclovir (which as noted above requires phosphorylation by HSV-TK) with HBPG (a HSV-TK inhibitor) to work, thus as noted above there is no motivation to combine these references. In addition, the present application provides surprising results regarding the combination of HBPG and acyclovir, as discussed in detail above, which would overcome any *prima facie* case of obviousness. For at least these reasons, the claimed compositions are not taught or suggested by Hostetler and Wright, alone or in combination. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C § 103.

Rejection under 35 U.S.C. §103(a) Wright et al. in view of Naesens

Claims 1-3, 7, 8, 10, 14, 16-18, 32-34, 36, 43, 45, and 50 were rejected as being allegedly obvious over Wright *et al.* '155 in view of Naesens et al., Herpes, 8(1), 2001 ("Naesens"). The Office Action states:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising a combination of an inhibitor of Herpes simplex virus thymidine kinase and an antiherpes substance comprising one or more of a (1) a pre-phosphorylated or phosphonate nucleoside analog, a pyrophosphate analog and a nucleoside analog since Wright et al. discloses pharmaceutical compositions comprising a herpes simplex virus thymidine kinase inhibitor and suggests the combination with other direct antiviral drugs (Office Action, page 16).

Thus, the Office Action alleges that Naesens, which "discloses a series of antiherpes substances including acyclovir, ganciclovir, foscarnet and brividin" (page 15 of the Office Action, last paragraph) provides teachings which are missing from Wright *et al.*, *e.g.* making a combination of an inhibitor of HSV-TK and an antiherpes substance. Applicant respectfully disagrees, and requests reconsideration in light of the following remarks.

The Office Action takes the position that one skilled in the art would have combined an oxo-guanine thymine kinase inhibitor with antiherpes agents based on Wright *et al.* in combination with Naesens (Office Action at page 10). Applicant respectfully disagrees. One skilled in the art would not have combined Naesens with Wright *et al.* for at least the reasons set forth above, *i.e.*, prior art studies showing that inhibitors of HSV TK were known to antagonize the antiherpes effect of nucleoside analogs that inhibit viral DNA replication; Naesens does not address, let alone refute, this understanding. Furthermore, as discussed above, the present Applicant has provided evidence of surprising results with regard to the combination of HBPG with acyclovir, cidofovir, or foscarnet."

For at least these reasons, Naesens does not supply what is missing in Wright *et al.*, and the presently claimed methods and compositions are not obvious over the cited art. Therefore, Applicant requests that the Examiner kindly reconsider and withdraw the rejection under 35 U.S.C. § 103.

CONCLUSION

For at least the reasons set forth herein, Applicant submits that all claims are in condition for allowance, and request early and favorable action thereon. If the Examiner feels it would expedite allowance, he is invited to telephone the undersigned at (617)956-5985.

The fee of $230 for a Petition for Extension of Time of Two Months is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. No other fees are believed due. However, please apply all charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-0183001.

Respectfully submitted,

Date: 10/6/09

Janice Kugler DeYoung
Reg. No. 50,429

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (877) 769-7945
22252390 (2).doc